Remarks

This amendment is being made pursuant to receipt of a Communication mailed in connection with the above-identified application on November 13, 2007. The Examiner correctly pointed out a typographical error in Claim 1, namely, the inadvertent deletion of "S" in the definition of variable Z_1. This typographical error has been corrected, with the effect being that Claim 1 is in the same form is was previously presented. Applicants have also amended Claim 26 to remove two benzenesulfonate compounds.

Interview with the Examiner

Applicants' undersigned representative held a telephonic interview with the Examiner on November 13, 2007. Although agreement on allowable subject matter was not reached, Applicants agreed to remove two benzenesulfonamide compounds from Claim 26. The Allen reference cited in an obviousness rejection was discussed, as well as the possibility of filing a Declaration to overcome the rejection. Finally, the withdrawn claims were discussed.

Applicants may file a Declaration under separate cover, although they believe the arguments presented herein should be sufficient to overcome the pending obviousness rejection.

Status of the Claims

Following amendment as requested herein, the following claims are now pending in the present application: 1, 11-16, 19-27, 32-40, and 43. Of these, Claims 36-40 and 43 were withdrawn. By this Amendment, Claim 26 is amended to remove the carboxamide compound and benzenesulfonate compounds not within the scope of Claim 1, from which Claim 26 depends.

Oath/Declaration

The Office Action stated that a new Oath or Declaration was required, to correct a typographical error in the filing date of PCT/GB02/02563. A new Declaration is attached, correcting this typographical error.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claim 26 was rejected under 35 U.S.C. §112, second paragraph, as indefinite. The basis for the rejection was that Claim 26, which depends from Claim 1, included a compound not within the scope of Claim 1 as amended. Claim 26 has been amended to remove this compound. Pursuant to a telephone conference with the Examiner, as mentioned above, two additional compounds were removed as well. Accordingly, the rejection should be withdrawn.

Rejections under 35 U.S.C. § 103(a)

Claims 1, 11-16, 19-27 and 32-35 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over EP 0 512 675 to Allen et al. ("Allen"). This rejection is respectfully traversed.

EP 0 512 675 discloses compounds that contain an imidazole ring (see Formula I), which corresponds to the X_1 to X_4-containing ring of the claimed compounds. The Office Action acknowledges that the presently-claimed compounds are distinguished from Allen in view of the fact that the 2-position of the imidazole ring (as defined by *"-ER^1"* in Claim 1 of EP 512 675 at pages 68 to 69) has to represent a substituent, whereas the 2-position in the imidazole ring in the claimed compounds is unsubstituted (i.e., is H).

The purported basis for the rejection (i.e., at pages 7 and 8 of the Office Action) is that the modification (i.e. replacing the 2-substituent with a hydrogen atom to provide a 2-unsubstituted imidazole) would be an obvious modification of the prior art to arrive at the present invention. This is on the basis that *"those skilled in [the] chemical art [would appreciate that] one homologue is not such an advance over [an] adjacent member of [the]*

series as requires invention because chemists knowing properties of one member of [the] series would in general know what to expect in adjacent members. The motivation to make the claimed compounds derives from the expectation that structurally similar compounds would possess similar activity (i,e, an ***angiotension II antagonist)"*** (emphasis added).

In this respect, Applicants respectfully point out a key difference between the disclosure of EP 512 675 and the present case. While the prior art document discloses angiotensin II (AngII) ***ant***agonists, the compounds of the present invention have found utility as being useful angiotensin II **agonists.**

The Examiner has provided no evidence to suggest why the skilled person would expect the pharmacological activity to completely change as a result of changing the prior art components to those presently claimed, nor indeed why that person would, when searching for compounds that act as Ang II agonists, start from a prior art document that related to Ang II antagonists.

The Office Action also appears to suggest that, because the prior art document states that the antagonists disclosed therein are useful for treating hypertension, it would be obvious that the presently-claimed compounds would also be useful in treating hypertension (which is one of the conditions presently claimed in this case).

Firstly, the Office Action has not provided any cogent argumentation in relation to why the claimed modification is obvious in a purely structural sense, taking the cited prior art document into consideration in isolation.

Secondly, the fact that the Applicant has surprisingly found that the presently-claimed, novel compounds are useful as Ang II agonists is a feature that is non-obvious *per se,* providing a completely different type of utility to those compounds disclosed in the cited prior art.

The Office Action states at page 7 of the action that *"It is well established that the substitution of a hydrogen atom for a lower alkyl on a known compound is not a patentable modification absent unexpected or unobvious results".* Surely, when such a modification

completely changes the nature of the pharmacological activity of the compounds, this has to be regarded as an unexpected and unobvious result. Indeed, this has to be put in the context of the fact that it is extremely rare in the pharmacological art to render compounds that are small molecules that have agonist activity at ***any*** receptor. Normally small molecules tend to have antagonist activity.

In this respect, the fact that similar diseases may be treated as a result of the newly found utility is, respectfully, largely irrelevant. There are many different ways of treating hypertension, just as there are many different ways of treating other diseases. When an inventor finds a new way of treating a known condition by way of making a structural modification that leads to a completely different class of activity in the treatment of the same condition, under U.S. patent law, this is a patentable invention.

Thus, the newly-discovered pharmacological effect provided by the present invention provides the public with a completely new invention, which could in no way have been derived from the cited prior art.

Thirdly, Applicants respectfully point out that, as stated in the application at page 6 to 9, the compounds presently claimed are not only agonists of AngII, but are, more specifically, agonists of the angiotensin II type 2 (the AT2) sub-receptor. In particular, they are agonists that bind selectively to that sub-receptor. This is positively demonstrated by way of the data described in Example 14 (see page 64), where it is stated that the compounds of the examples were all found to exhibit an affinity for AT2 receptors of less than Ki = 100 nM and an affinity for the other angiotensin II receptor (AT1) of more than Ki = 500 nM. Thus, this activity could in no way have been predicted from what was known from the cited prior art or other prior documents which the applicants are aware.

Hence, not only is there no suggestion in the cited prior art document of the utility of the compounds disclosed therein as Ang II agonists, there is further no suggestion of their utility as, specifically, selective AT2 sub-receptor agonists. The rejection should be withdrawn on this basis alone.

Further, since EP 0 512 675 mentions, with particularity, the importance of the substitution at a specific position on the imidazole ring, it teaches away from removing the substitution on the imidazole ring at this position (i.e., by replacing the substituent ER^1 with H). Variables R^3, R^4, and R^{9-13} in the cited reference provide for optional substitution at every position on each of the three rings (i.e., the imidazole ring, the phenyl ring, and the heteroaryl ring), with the sole exception of the position where the moiety ER^1 is located. This position, located on the imidazole ring between the two ring nitrogens, is the only position in all three rings which has a mandatory substituent, and this is precisely the position where Applicants' claimed compounds include a hydrogen (i.e., are unsubstituted).

As a matter of patent law, the importance of this mandatory substitution simply cannot be overlooked, particularly since the cited reference, EP 0 512 675, does not overlook its importance. A prima facie case of obviousness would require, at a minimum, that the cited reference disclose a "homologous" substituent at a position it does not teach as being a mandatory substituent, and that the reference teach that the compounds have the same activity as the claimed compounds. Where, as here, the cited reference teaches that is mandatory to have a substituent (i.e., ER^1) at this position, and that the compounds have an entirely different pharmacological activity than the claimed compounds, Appliants respectfully assert that the Examiner has not set forth a *prima facie* case of obviousness.

EP 0 512 675 clearly states (page 2, lines 23-25) that the prior art failed to teach substituted imidazoles bonded to the various phenyl and thiophene or other rings. It further states (page 2, line 35) that its invention is directed to substituted imidazoles, with substitution specifically at the specified positions (page 2, lines 39-42). Since the only position on the imidazole ring that is specified as having a substituent is exactly the position where the instantly claimed compounds have no substituent, the cited reference teaches away from modifying the compound to arrive at the claimed compounds. Teaching away is the antithesis of obviousness, and therefore, the obviousness rejection should therefore be withdrawn.

Rejoinder of Process for Preparation Claims/

Presentation of Method of Treatment Claims

As discussed with the Examiner in the telephonic interview held on April 5, 2007, Applicants would be permitted to rejoin process for preparation claims, and the Examiner would consider certain method of treatment claims, directed to the compounds the Examiner agreed were allowable (i.e., if Claim 1 was amended to incorporate the limitations of Claim 18). Now that the Examiner has rejected Claim 1, amended as previously agreed, and Applicants arguments are believed to overcome that rejection, Applicants respectfully request that such process for preparation and method of treatment claims be considered and found to be allowable.

Should the Examiner be inclined to allow the compound claims, but consider the method claim to be unpatentable for any reason, she is encouraged to contact the undersigned Applicants' representative to discuss changes that might be made to these claims so that the application is in condition for allowance.

Conclusion

In view of the amendments and comments presented herein, Applicants respectfully submit that the application is in condition for allowance, and prompt notification of same is earnestly solicited.

The Examiner is encouraged to contact the undersigned with any questions she may have, and if the Examiner is not inclined to allow any or all of the claims, to also issue an Advisory Action providing reasons for such non-allowance.

The Director is hereby authorized to charge any fee that may be required, if any, to Womble Carlyle's Deposit Account No. 09-0528.

Respectfully submitted,

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